Pioglitazone and bariatric surgery are the most effective treatments for non-alcoholic steatohepatitis: A hierarchical network meta-analysis

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Abstract: AIMS To compare different treatments for non-alcoholic steatohepatitis (NASH) and to determine an effectiveness hierarchy. MATERIALS AND METHODS We conducted a systematic review and Bayesian network meta-analysis including randomized controlled trials or prospective trials with at least 6 months' follow-up and histologically proven NASH in adult participants. Monte Carlo simulations were performed, each generating 10 000 data points, and results are reported as medians and 95% credibility intervals (CrIs). A meta-regression was conducted to find the effects of body mass index (BMI) decrement or reduction of homeostatic model assessment of insulin resistance (HOMA-IR) index on non-alcoholic fatty liver disease activity score (NAS) change. RESULTS The review identified 48 eligible trials comprising 2356 adults (55.6% men). Data were pooled using a random-effects model. The most effective treatments in terms of NAS reduction per semester were pioglitazone and Roux-en-Y gastric bypass (RYGB; -1.50 [95% CrI -2.08, -1.00] for pioglitazione and -1.00 [95% CrI -1.70, -0.32] for RYGB). Pioglitazone was also the best therapy for steatosis and lobular inflammation reduction. RYGB was the best treatment for hepatocellular ballooning reduction, whereas antioxidants appeared to be best for fibrosis improvement. For each 1% decrement in BMI, NAS was reduced by 1.3% (= 1.28%, P = 0.01). Conversely, a 1% reduction of HOMA-IR index reduced NAS by 0.3% (= 0.31%, P < 0.001). Treatments that were regarded as promising, such as elafibranor, simtuzumab, selonsertib, cenicriviroc, obeticholic acid and liraglutide, did not reduce either NAS or liver fibrosis significantly. CONCLUSIONS Pioglitazione and RYGB are the most effective therapies for NASH. Antioxidants may be effective in reducing liver fibrosis. Weight loss and improvement of hepatic insulin resistance are promising approaches in the treatment of NASH.

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ORIGINAL ARTICLE

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Pioglitazone and bariatric surgery are the most effective treatments for non-alcoholic steatohepatitis: A hierarchical network meta-analysis

Simona Panunzi PhD[1] | Sabina Maltese PhD[2] | Ornella Verrastro PhD[3,4] | Luca Labbate PhD[2] | Andrea De Gaetano PhD[1] | Maurizio Pompili MD[3,4] | Esmeralda Capristo MD[3,4] | Stefan R. Bornstein MD[5,6] | Geltrude Mingrone MD[3,4,6]

[1]CNR-IASI, Laboratorio di Biomatematica, Consiglio Nazionale delle Ricerche, Istituto di Analisi dei Sistemi ed Informatica, Rome, Italy

[2]CNR-IRIB, Consiglio Nazionale delle Ricerche, Istituto per la Ricerca e l'Innovazione Biomedica, Palermo, Italy

[3]Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

[4]Università Cattolica del Sacro Cuore, Rome, Italy

[5]Department of Medicine III, Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden, Dresden, Germany

[6]Division of Diabetes and Nutritional Sciences, Faculty of Life Sciences and Medicine, King's College London, London, UK

Correspondence
Geltrude Mingrone, MD, PhD, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo A. Gemelli 8, Università Cattolica del Sacro Cuore, 00168, Rome, Italy. Division of Diabetes and Nutritional, Sciences, Faculty of Life Sciences and Medicine, King's College, London, SE5 9NU London, UK.
Email: geltrude.mingrone@unicatt.it; geltrude.mingrone@kcl.ac.uk

Funding information

Abstract

Aims: To compare different treatments for non-alcoholic steatohepatitis (NASH) and to
determine an effectiveness hierarchy.

Materials and Methods: We conducted a systematic review and Bayesian network meta-analysis including randomized controlled trials or prospective trials with at least 6 months' follow-up and histologically proven NASH in adult participants. Monte Carlo simulations were performed, each generating 10 000 data points, and results are reported as medians and 95% credibility intervals (CrIs). A meta-regression was conducted to find the effects of body mass index (BMI) decrement or reduction of homeostatic model assessment of insulin resistance (HOMA-IR) index on non-alcoholic fatty liver disease activity score (NAS) change.

Results: The review identified 48 eligible trials comprising 2356 adults (55.6% men). Data were pooled using a random-effects model. The most effective treatments in terms of NAS reduction per semester were pioglitazone and Roux-en-Y gastric bypass (RYGB; −1.50 [95% CrI −2.08, −1.00] for pioglitazione and −1.00 [95% CrI −1.70, −0.32] for RYGB). Pioglitazone was also the best therapy for steatosis and lobular inflammation reduction. RYGB was the best treatment for hepatocellular ballooning reduction, whereas antioxidants appeared to be best for fibrosis improvement. For each 1% decrement in BMI, NAS was reduced by 1.3% (β = 1.28%, P = 0.01). Conversely, a 1% reduction of HOMA-IR index reduced NAS by 0.3% (β = 0.31%,

$P < 0.001$). Treatments that were regarded as promising, such as elafibranor, simtuzumab, selonsertib, cenicriviroc, obeticholic acid and liraglutide, did not reduce either NAS or liver fibrosis significantly.

Conclusions: Pioglitazione and RYGB are the most effective therapies for NASH. Antioxidants may be effective in reducing liver fibrosis. Weight loss and improvement of hepatic insulin resistance are promising approaches in the treatment of NASH.

KEYWORDS
bariatric surgery, fatty liver disease, systematic review

1 | INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) represents the most common chronic liver disease in industrialized countries.[1] Its prevalence in adults is 25% to 30%, reaching values of 50% to 75% in subjects with obesity and 65% to 90% in those with type 2 diabetes.[2] NAFLD encompasses a spectrum of liver pathologies with different clinical prognoses, ranging from simple steatosis (non-alcoholic fatty liver) to non-alcoholic steatohepatitis (NASH).[3]

It is estimated that approximately 10% to 30% of patients with NAFLD have underlying NASH, and among patients with NASH, up to 10% to 15% will subsequently develop cirrhosis.[3] Furthermore, among non-cirrhotic subjects, those with NASH have a higher risk of hepatocellular carcinoma compared to other aetiologies of chronic liver disease.[4] NASH is currently the third most common indication for liver transplantation and is predicted to become the most common within the next two decades.[3]

In subjects with NASH overall mortality is increased by approximately 70%, and mortality due to cardiovascular disease is increased by approximately 300% compared to subjects without NASH.[5]

Reversal of NASH or a decrease in disease activity (NAFLD Activity Score [NAS]) is likely to reflect a reduction of the risk of progression to cirrhosis as well as a decrease in the risk of cardiovascular complications, including mortality. An improvement in NASH has also been associated with an improvement in liver fibrosis, whereas patients with worsening of NASH were also more prone to fibrosis progression.[6] NASH-induced liver fibrosis per se is associated with increased morbidity and mortality.[7,8] Lifestyle intervention (low-calorie diet and physical exercise) remains the cornerstone of NASH management because it reduces body weight and improves insulin resistance, which are the primary triggers of this disease.[9] However, adherence to these measures is poor. Therefore, a great deal of effort is being made to develop drugs targeting NASH and/or liver fibrosis. Several drugs have already been tested, while others are in late-stage testing, and many more others are in the pipeline. The global market for new drugs against NASH is, in fact, projected to be approximately $35 bn per year by 2025.[10]

Currently, no specific drugs are licensed to treat NASH.[3] Although different pharmacological treatment options are available, a completely safe and effective therapy for NASH has not yet been identified.

Previous trial-based meta-analyses[11–13] did not include new drugs, such as elafibranor, simtuzumab, selonsertib, cenicriviroc and liraglutide, because results have been only recently released. In addition, the above meta-analyses[11–13] targeted only randomized controlled trials (RCTs) while longitudinal studies, despite large sample sizes and adequate follow-up, such as those in bariatric surgery, were disregarded.

The results of many recent RCTs were negative regarding the intention-to-treat analysis of the primary outcome, while confounding post hoc analyses stated the benefits of new drugs. In addition, arbitrary and more convenient definitions of NASH that are not based on canonical histological features and NAS score were used in different papers. This means that, in order to retrieve important information on the efficacy of a drug used to treat NASH, readers need to go carefully through the entire manuscripts. A meta-analysis is a way to synthetize a huge number of results and, if a hierarchical analysis is performed, to list in order of effectiveness drugs with proven efficacy.

The aim of the present meta-analysis was to assess several current therapeutic options, tested in RCTs or generic prospective trials with a follow-up of at least 6 months. The endpoints we focused on were improvement of histological NAS or improvement of single NAS components (steatosis, ballooning and inflammation) as well as fibrosis, ranking the treatments in relation to their effectiveness. A further analysis was conducted to assess therapies that reduced NAS by at least two points, in terms of percentage of responders.

2 | METHODS

2.1 | Search strategy and study selection

We searched MEDLINE (PubMed), Scopus, EMBASE, Web of Science, the Cochrane Central Register of Controlled Trials, and clinicaltrials.gov from inception to 30 September 2019, without language restrictions. Books of abstracts from annual meetings of the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases were also screened from 2000 to 2019 (NAFLD sections).

Eligible RCTs or prospective trials with at least 6 months' follow-up and histologically proven NASH in adult participants (age ≥ 18 years) were identified. The abstracts were screened by three independent reviewers (S.M., S.P. and O.V.), who also extracted the data. Disagreements between investigators were resolved by discussion. The search strategy is reported in the Supporting Information.

The study protocol was published on the PROSPERO international prospective register of systematic reviews (registration number CRD42019143166). Ethical approval for this evidence synthesis was not required.

2.2 | Patient involvement

We involved patients in the study design, including identifying the original research question and the necessity to perform a systematic review and meta-analysis on NASH therapy.

2.3 | Study quality evaluation

Forty-eight studies were included in the meta-analysis (Supporting Information Table A1). For each study the risk of bias was estimated according to the Cochrane Collaboration's risk-of-bias tool.[14] The risks of bias considered were "random sequence generation", "allocation concealment", "blinding of participants and personnel", "blinding outcome assessment", "incomplete outcome data", "selective reporting" and "other". For each risk, the judgment (low risk, unclear risk, high risk) for each trial is given, along with a descriptive justification for the judgment. The judgments were made by two independent statisticians.

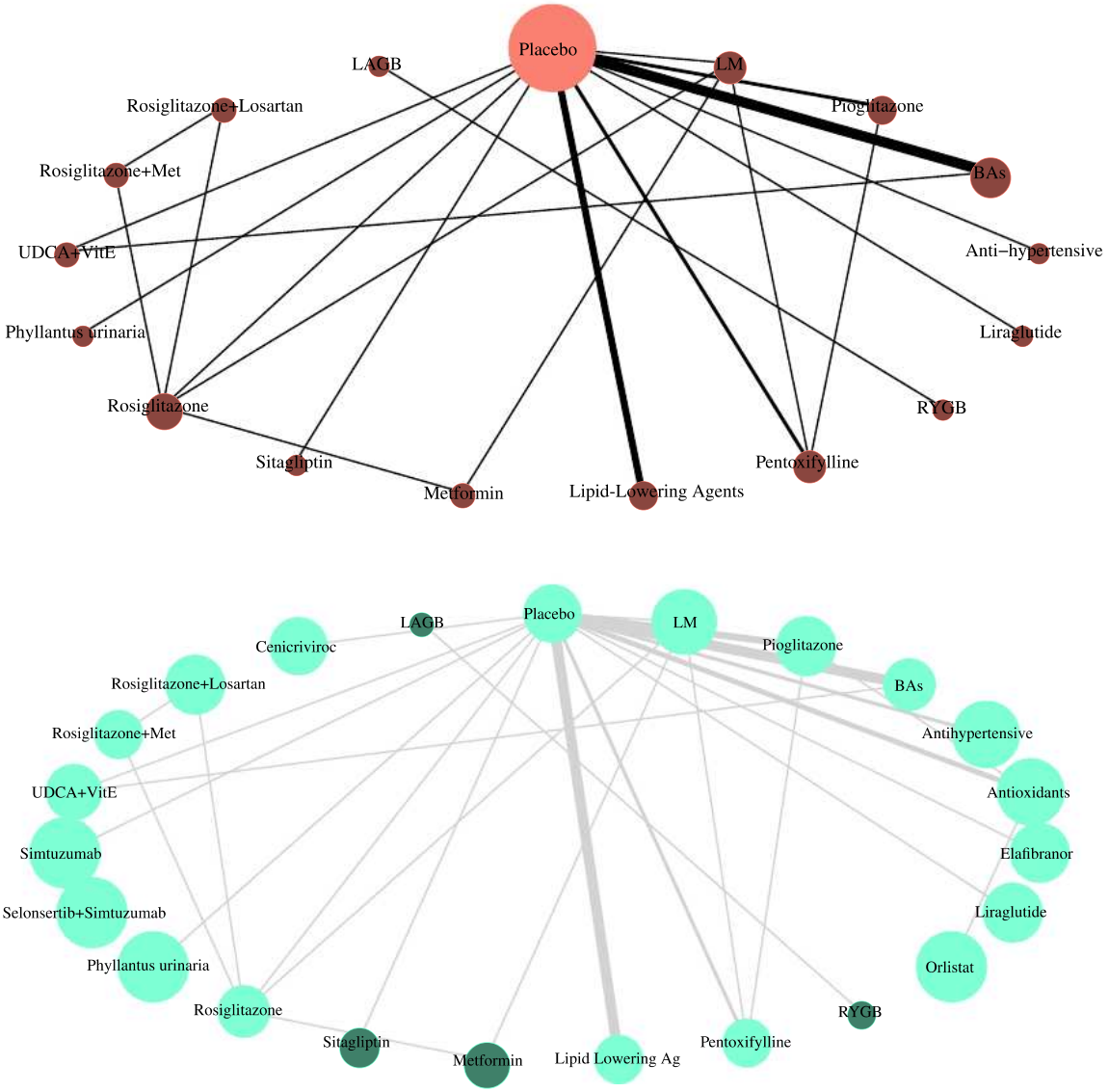
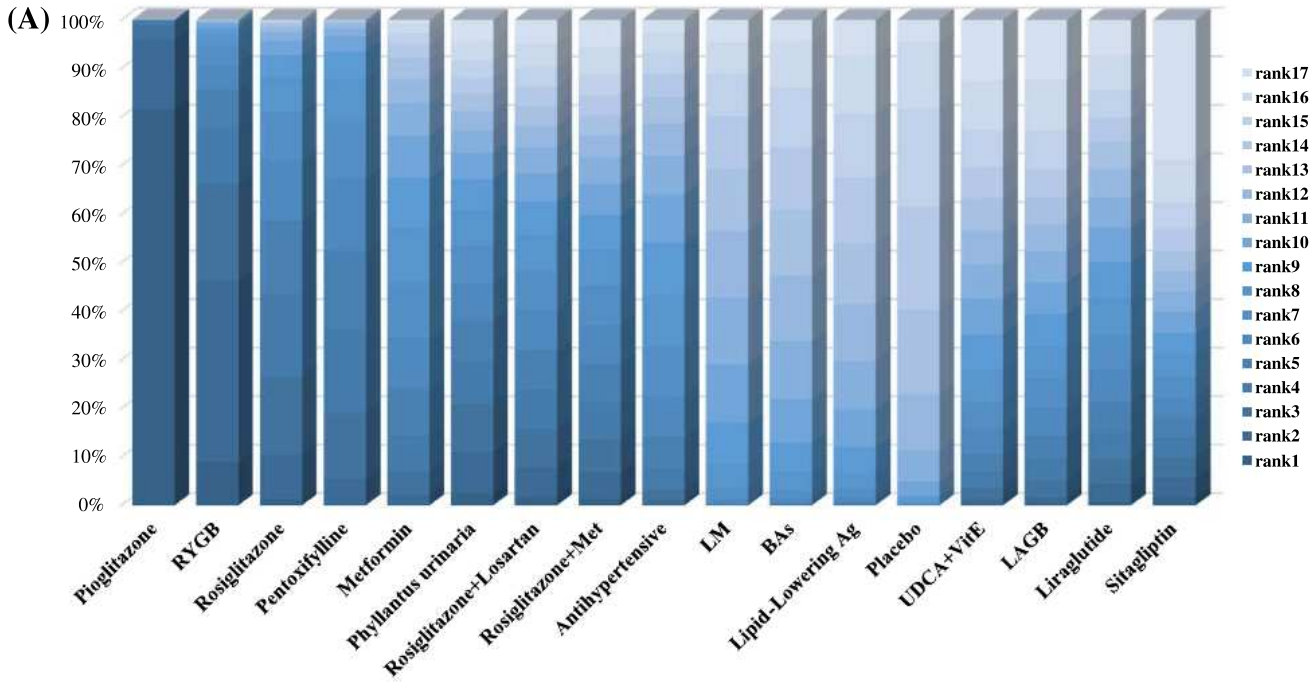


FIGURE 1 Network plot including 30 studies for the non-alcoholic fatty liver diease activity score (NAS) outcome and highlighting the relationships among the treatments. The thickness of the lines (edges) is proportional to the number of studies involved in the direct comparison between each pair of treatments. The size of the nodes represents the number of times the treatment is involved in a direct comparison with any other treatment for the NAS outcome evaluation (A). Network including all studies and highlighting the relationships among the treatments. The thickness of the lines (edges) is proportional to the number of studies involved in the direct comparison between each pair of treatments. The size of the nodes represents the acceptability rate per semester, that is, the complement of the dropout percentage. Large nodes represent treatments with a small percentage of study dropouts (B). BAs, bile acids; RYGB, Roux-en-Y gastric bypass; LAGB, laparoscopic adjustable gastric band; Met, metformin; UDCA, ursodeoxycholic acid; VitE, vitamin E



(B)

	rank1	rank2	rank3	rank4	rank5	rank6	rank7	rank8	rank9	rank10	rank11	rank12	rank13	rank14	rank15	rank16	rank17
Pioglitazone	**0.82**	0.14	0.03	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
RYGB	0.09	**0.37**	0.20	0.12	0.08	0.05	0.04	0.02	0.01	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Rosiglitazone	0.01	0.09	**0.16**	0.17	0.15	0.12	0.10	0.07	0.05	0.03	0.02	0.01	0.01	0.00	0.00	0.00	0.00
Pentoxifylline	0.00	0.05	0.14	**0.17**	0.16	0.15	0.12	0.09	0.05	0.03	0.02	0.01	0.00	0.00	0.00	0.00	0.00
Metformin	0.00	0.02	0.05	0.07	**0.10**	0.11	0.11	0.11	0.10	0.09	0.07	0.05	0.04	0.03	0.02	0.02	0.01
Phyllantus urinaria	0.02	0.09	0.10	0.09	0.08	**0.08**	0.08	0.07	0.06	0.05	0.05	0.04	0.04	0.03	0.04	0.04	0.04
Rosiglitazone+Losartan	0.02	0.06	0.08	0.08	0.08	0.08	**0.08**	0.08	0.07	0.06	0.05	0.04	0.04	0.04	0.04	0.05	0.05
Rosiglitazone+Met	0.01	0.06	0.07	0.08	0.08	0.08	0.08	**0.08**	0.07	0.06	0.05	0.05	0.04	0.04	0.05	0.06	0.06
Anti-hypertensive	0.00	0.01	0.02	0.04	0.07	0.08	0.10	0.11	**0.11**	0.10	0.08	0.07	0.06	0.05	0.04	0.04	0.03
LM	0.00	0.00	0.00	0.00	0.00	0.01	0.02	0.05	0.08	**0.12**	0.14	0.14	0.13	0.11	0.09	0.07	0.05
BAs	0.00	0.00	0.00	0.00	0.00	0.01	0.02	0.04	0.06	0.09	**0.12**	0.14	0.14	0.13	0.12	0.10	0.04
Lipid Lowering Ag	0.00	0.00	0.00	0.00	0.00	0.01	0.02	0.03	0.06	0.08	0.10	**0.12**	0.13	0.14	0.13	0.12	0.07
Placebo	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.03	0.06	0.12	**0.18**	0.21	0.20	0.14	0.05
UDCA+VitE	0.00	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.07	0.07	0.07	0.07	0.07	**0.06**	0.08	0.10	0.13
LAGB	0.00	0.01	0.04	0.04	0.05	0.06	0.06	0.06	0.07	0.07	0.06	0.06	0.05	0.06	**0.08**	0.11	0.12
Liraglutide	0.01	0.04	0.05	0.06	0.06	0.07	0.07	0.08	0.08	0.07	0.06	0.06	0.05	0.05	0.06	**0.07**	0.07
Sitagliptin	0.02	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.05	0.04	0.04	0.04	0.04	0.05	0.06	0.09	**0.29**

FIGURE 2 Rank probabilities plot (A) and rank probabilities table (B) of the treatments for the estimated normalized effect size post- minus pretreatment on the non-alcoholic fatty liver diease activity score (NAS) outcome. The treatments are listed according to their rank. The most effective treatments for NAS reduction are first in the list:on the left in (A) and at the top in (B). The values in the main diagonal correspond to the rank in which the treatments show the highest probabilities to belong. BAs, bile acids; RYGB, Roux-en-Y gastric bypass; LAGB, laparoscopic adjustable gastric band; LM, festyle modifications; Met, metformin; UDCA, ursodeoxycholic acid; VitE, vitamin E

2.3.1 | Statistical analysis

We report the network meta-analysis (NMA) according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) extension statement for network meta-analyses.[15]

Descriptive of quantitative variables was computed, weighting by study size.

To take into account the different duration of the studies each outcome was evaluated in terms of effect per semester.

For each outcome a Bayesian NMA was performed to estimate the effects of treatment and to compute direct and indirect comparisons among different therapies for NASH. The NMA is based on Monte Carlo simulations with the use of a normal model and an identity link. In the present study each NMA was performed by using non-informative N(0, 1000) priors for the treatment-specific fixed effects and a random-effect model to pool data. Variances of the random effects were assumed as homogenous and with priors following a uniform distribution. Ten thousands iterations were performed and the potential scale reduction factors (PSRFs), with the corresponding upper confidence limits, together with the trace plots were used for convergence diagnostics. The PSRFs were calculated for each treatment effect and for differences between each pair of treatments.

The results of each NMA are reported as medians and 95% credibility intervals (CrIs).

The network inconsistency was evaluated by means of a node-splitting approach based on Monte Carlo Markov Chain simulations, considering random-effect models, normal priors for treatment fixed effects, as well as uniform priors for the variances of the random effects. This method in fact allows indirect evidence to be separated from direct evidence when comparing each pair of treatments. The discrepancy between the estimated mean differences between each pair of treatments using direct and indirect evidence indicates the level of network inconsistency. *P* values are reported to indicate possible statistically significant discrepancies.

Possible publication bias was investigated by means of the funnel plot. The studies entered in the analysis were those in which a treatment was compared with placebo. The random mixed effect version of the Egger test was used to assess the presence of funnel plot asymmetry.

An NMA was also conducted on a set of 14 studies (for a total of 1683 patients, 48.7% men) including studies already evaluated in the above analyses as well as other studies, all of which reported treatment evaluation through percentage of responders (responders being defined as those presenting a reduction of NAS by at least two points).

The acceptability rate is, in the present study, defined as the compliance to treatment, therefore patients who discontinued treatment are considered dropouts. The proportion of patients per semester who dropped out for any reason, was computed as a weighted average over the treatments.

The evaluated effect size in the first set of NMAs was the difference post- minus pre- treatment of the considered outcomes $\delta = x_{post} - x_{pre}$.

When a study did not report the standard deviation (SD) of the effect size, it was imputed by computing the following quantity: $\sigma_{diff} = \sqrt{\sigma_{pre}^2 + \sigma_{post}^2 - 2\rho\sigma_{pre}\sigma_{post}}$, [18] with ρ being the empirical correlation between pre- and post-treatment mean values over all the considered studies ($\rho = corr[x_{post,}\ x_{pre}]$). In order to assess if the estimates of the mean SD could affect the final results, a sensitivity analysis was carried out by considering increments and decrements of the ρ coefficient by 20%.

Standard deviation was also computed from 95% confidence intervals (CIs) for δ: when studies reported only the *P* value associated to a test conducted for assessing if δ (post-pre) was significantly different from zero, the SD was computed as $|\delta|\sqrt{n-1}/t_{inv}(P,n-1)$, with t_{inv} being the inverse of the two-tailed *t*-distribution.

When mean values of post- and/or pretreatment could not be obtained from the original studies, they were replaced by median values, when present, and the corresponding SD values were computed using two different approaches: if the interquartile range was reported then the formula $\sigma = \frac{IQR*3}{4}$ was adopted; when the studies recorded the value range instead, the SD was calculated according to the formula $\sigma = \frac{Max-Min}{6}$.

For NAS score the percent variation with respect to baseline, per semester, was also considered as an additional effect size in the NMA analysis. Computation of the SD values of the percent variations was performed by using the delta method.[16]

A meta-regression was conducted to study any possible relationship between percent reduction of NAS score and percent reduction in body mass index (BMI) and homeostatic model assessment of insulin resistance (HOMA-IR). All the measures were evaluated for semester. For each meta-regression, a leave-one-out cross-validation procedure (LOOCV), followed by bootstrapping with 10 000 sampling with replacement, was performed to validate each meta-regression coefficient estimate and variability. The mean and SD from the cross-validation samples were obtained and compared with the bootstrapping distribution. All the statistical analyses were conducted in R[17]: the *pcnetmeta*[18] package was used for NMA analysis.

3 | RESULTS

For the primary outcome (variation in NAS), 30 studies (2356 patients, 55.6% men) were included in the analysis; secondary outcomes were variations of steatosis (30 studies, 1751 patients, 58.9% men), fibrosis (35 studies, 2203 patients, 55.0% men), hepatocellular ballooning (30 studies, 1810 patients, 58.6% men) and lobular inflammation (32 studies, 1879 patients, 58.3% men), alanine aminotransferase (ALT; 41 studies, 3434 patients, 51.5% men), aspartate aminotransferase (AST; 36 studies, 3140 patients, 51.5% men) and gamma-glutamyl transferase (GGT; 24 studies, 2654 patients, 50.3% men).

The agreement between investigators for trial eligibility was excellent (κ statistic = 0.95).

The flow chart in the Supporting Information (Figure A1) shows the selection process and Supporting Information Table A1 reports all the studies included in the meta-analysis. Supporting Information - Table A2 shows weighted means and SDs of the quantitative variables collected from the different studies.

3.1 | Study quality assessment

The risks of bias, together with the respective judgments, are reported in the risk tool in Supporting Information Table A3. A risk-of-bias graph is reported in Supporting Information Figure A2(A), and a risk-of-bias summary is reported in Supporting Information Figure A2(B). The most frequently observed low risk was "blinding outcome assessment", followed by "selective outcome reporting" and "incomplete outcome data". The source of bias with the largest risk was "blinding of participants and personnel".

3.2 | Effectiveness

Figure 1A shows the network plot of the 30 studies used to compute the NAS outcome, and highlights the relationships among the treatments investigated. Figure 1B, reports the acceptability rate per semester.

The highest dropout rates were recorded for laparoscopic adjustable gastric band, with a 25% dropout rate per semester, followed by

RYGB and sitagliptin, which were associated with approximately 23.4% and 16.7% dropout rates per semester, respectively.

Considering the per-semester normalized effect size post- minus pretreatment, Figure 2 shows the rank probabilities plot (Figure 2A) and the corresponding rank probabilities table (Figure 2B) on the NAS outcome for all treatments. The treatments are listed according to their rank. The most effective treatments for NAS reduction were pioglitazone, RYGB and rosiglitazone. For these treatments the probabilities of ranking first, second, and third, respectively, in order of effectiveness were 82% for pioglitazone, 37% for RYGB and 16% for rosiglitazone. Supporting Information Table A4 reports the estimated treatment effects per semester (as median differences between post- and pre- mean values for each treatment). Sitagliptin was the least effective treatment in terms of NAS reduction: the estimated effect was in fact not significant. The estimated median of the differences post- minus pretreatment for pioglitazone, RYGB and rosiglitazone were −1.81 (95% CrI −2.35;−1.32), −1.30 (95% CrI −1.94;−0.70) and −1.01 (95% CrI −1.55;−0.43), respectively. The sensitivity analysis performed by letting ρ vary by 20% around its empirical estimate (0.69) showed no evident effect of the uncertainty on ρ for the determination of the 95% CrI of the medians. Figure 3A reports a forest plot showing the median 95% CrIs obtained with the empirical estimate ρ, together with the CrIs obtained with the 20% increment and decrement of ρ. Trace plots of the estimated effects obtained using three Markov chains Monte Carlo simulation show that the Bayesian posterior distributions of the effects of treatments are stationary. As an example, Supporting Information Figure A3 shows the trace plots for the first four treatments that performed better in terms of efficacy in reducing NAS. The RYGB trace plot shows the highest variability, even though the relative PSRF and its upper confidence limit are equal to 1.0 and 1.01, respectively. The average PSRF values for all treatment effects and for all the differences between two treatments are 1.02 and 1.01, respectively, and the corresponding upper limits are 1.06 and 1.03.

When percent variation was considered as effect size, the most effective treatments in terms of NAS reduction were RYGB (−35.1%, 95% CrI −46.0,−23.8), followed by pioglitazone (−31.9%, 95% CrI −41.3,−22.9) and rosiglitazone (−20.6%, 95% CrI −30.8,−9.59; Supporting Information Table A5). Figure 3B shows the corresponding forest plots for the percentage differences.

When compared with placebo, the most effective treatments in terms of NAS reduction were pioglitazone and RYGB, with an estimated effect difference median of − 1.50 (95% CrI−2.08,−1.00) for pioglitazone and −1.00 (95% CrI −1.70,−0.32) for RYGB. For both of these the CrI did not include the zero value (Supporting Information - Table A6). Comparisons of treatments in terms of percent NAS reductions are reported in Supporting Information Table A7.

3.3 | Inconsistency and publication bias

Figure 4A shows the estimated mean differences between each pair of treatments resulting from direct, indirect and all available evidence in the network. No comparisons were significant, indicating absence of inconsistency. Figure 4B shows the funnel plot for those studies in

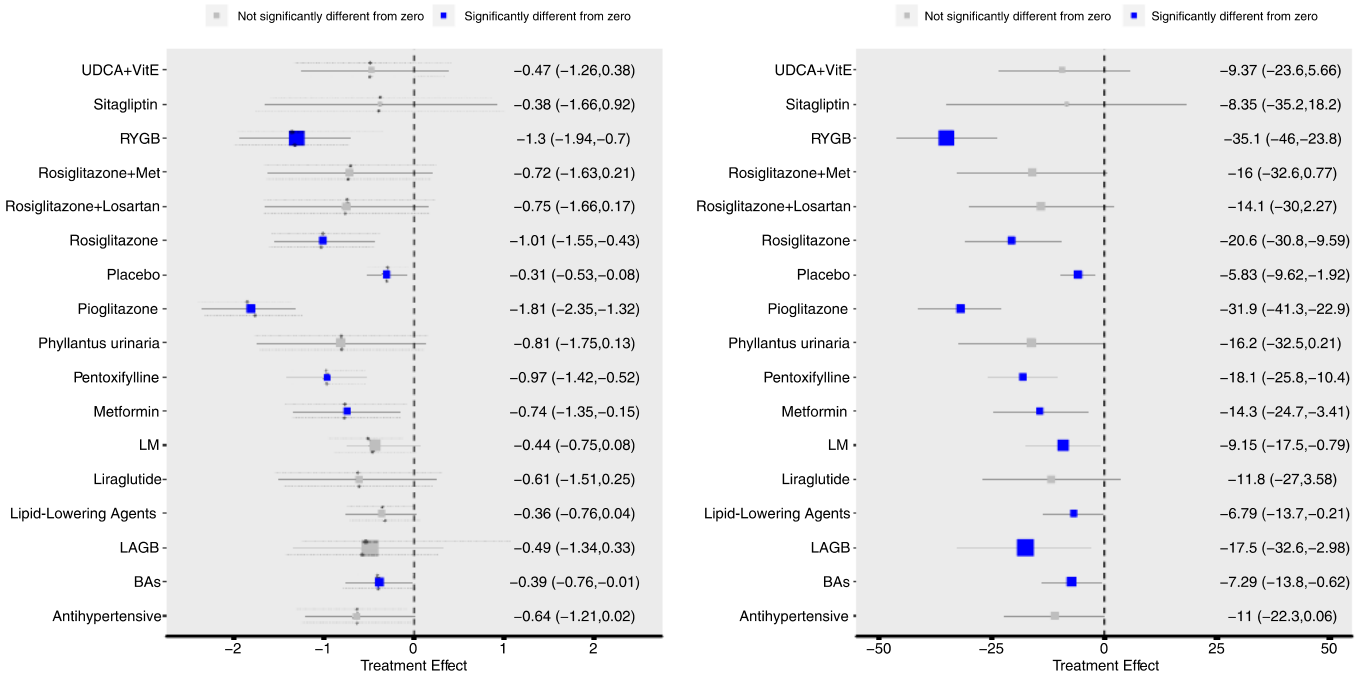


FIGURE 3 Forest plots for the absolute (A) and percent variations (B), per semester, of the non-alcoholic fatty liver diease activity score (NAS) score. Squares represent the estimated medians of the NAS variations (treatment effect). The median 95% credibility intervals (CrIs) are also reported. Grey squares and blue squares are not significantly and significantly different from zero treatment effects, respectively. (A) Shows results from the sensitivity analysis in terms of CrIs obtained by varying the empirical estimate ρ of 20% (see Methods)

which a treatment was compared with placebo. The plot is symmetrical and the Egger's regression test for asymmetry confirms the absence of publication bias (P = 0.98). The occurrence of observations outside the 95% CI is attributable to a variety of effects in comparison with placebo.

3.4 | Secondary outcomes

A Bayesian NMA was also performed for each secondary outcome. Supporting Information Table A8 shows the first three ranks that each treatment occupies in relation to each outcome (absolute differences). It also reports the differences in the estimated effects with respect to placebo along with the relative CrIs. Pioglitazone was the best therapy for steatosis, lobular inflammation and GGT reduction; RYGB emerged as the best treatment for the hepatocellular ballooning outcome, whereas antioxidants appeared to be the first choice for fibrosis improvement. Orlistat was the best treatment for reducing AST and ALT. All the above treatments were significantly superior to placebo except for orlistat and pioglitazone for the GGT outcome.

3.5 | Meta-regression analysis

Figure 5 reports the relationship between percent reduction of NAS as a function of percent reduction of BMI or HOMA-IR per semester. For each decrement of 1% point in BMI an average decrement of 1.3% points in NAS was found (β = 1.28%, standard error [SE] 0.52; P = 0.01 [Figure 5A]). The sample mean and SD obtained using the LOOCV procedure were 1.28 and 0.11, respectively, the average β obtained by bootstrapping was 1.10 and the SD was 0.9 (95% CI 0.25–4.1). For each decrement of 1% point in HOMA-IR index an average decrement of 0.3% points in NAS was obtained (β = 0.31%, SE 0.07; P < 0.001) (Figure 5B). The validation procedure confirmed these results: the sample mean and SD from LOOCV were 0.31 and 0.01, respectively, and the average estimate from bootstrapping was 0.31, with an SE of 0.08 (95% CI 0.13–0.44).

3.6 | Proportion of responders

Antihypertensive agents, pentoxifylline and *Phyllanthus urinaria* were the best treatments in terms of percentage of responders (absolute "risk" for NAS reduction of at least two points); however, odds ratios with respect to placebo were not significant (Supporting Information Figure A4).

3.7 | Adverse events

Supporting Information Table A9 summarizes the average percentage of patients who experienced adverse events associated with NASH treatments.

Rosiglitazone, placebo, pioglitazone and simtuzumab determined weight gain (50%, 12.45%, 2.70% and 1.41%, respectively).

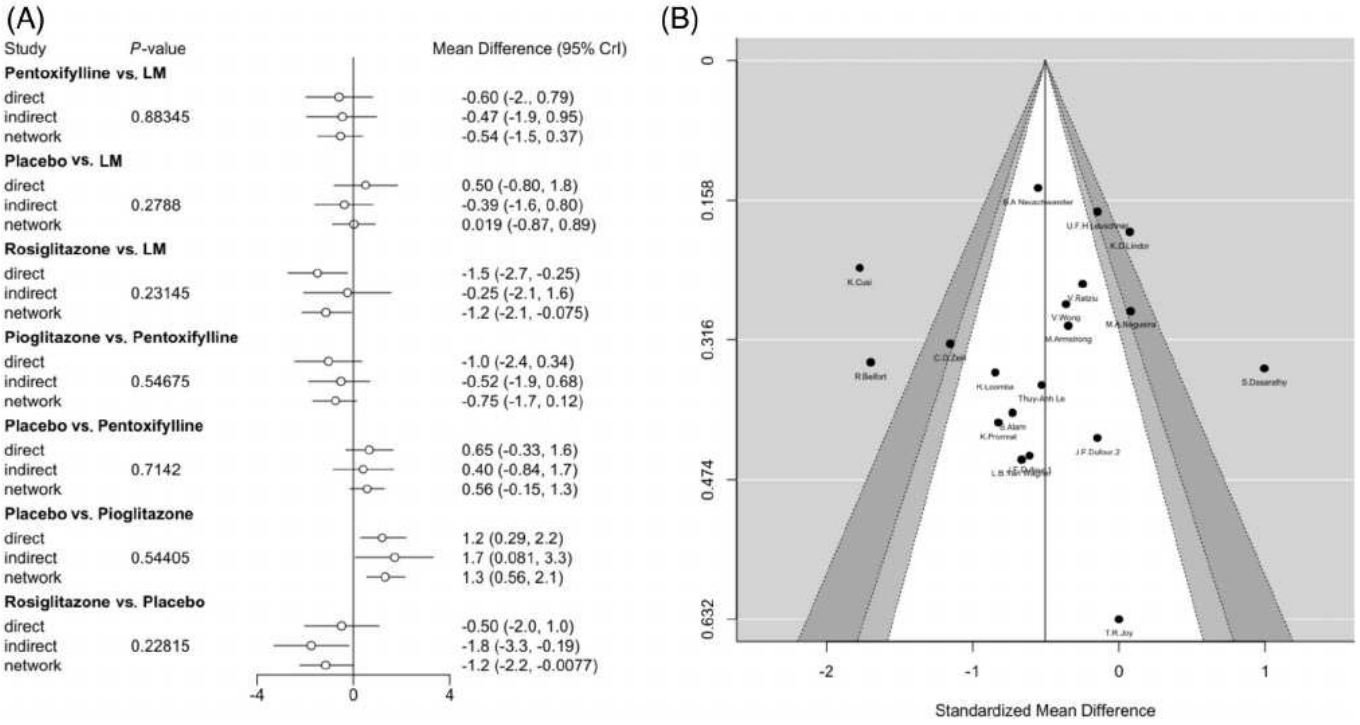


FIGURE 4 Estimated mean differences between each pair of treatments resulted from direct, indirect and all available evidence (network). P values for comparisons (testing network inconsistency) are also reported (A). Funnel plot including only studies where a treatment was compared with placebo. Light grey and dark grey bands are 95% and 99% confidence intervals, respectively (B) LM, lifestyle modifications

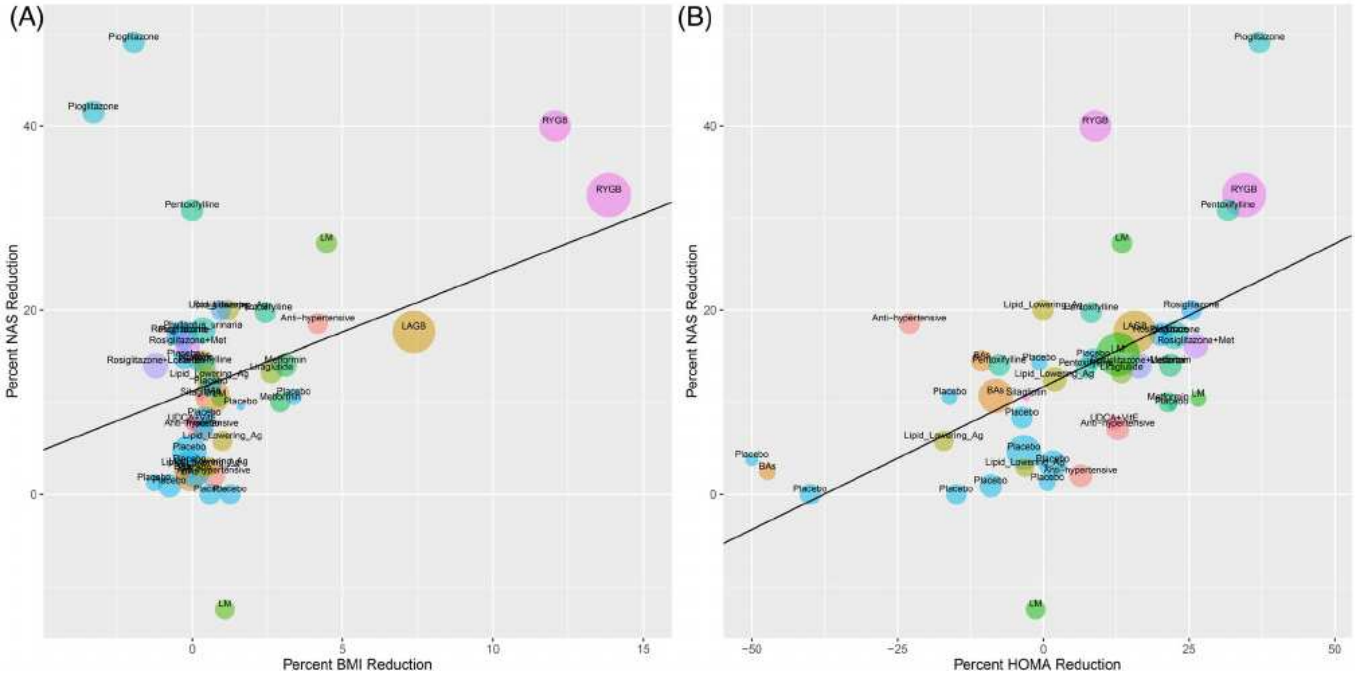


FIGURE 5 Relationship between percent non-alcoholic fatty liver diease activity score (NAS) variation with percent body mass index (BMI) variation (A) and homeostatic model assessment of insulin resistance (HOMA-IR) variation (B). Straight lines are predictions from meta-regression analyses. Each circle represents the effect (NAS variation) of a treatment at a certain value of the independent variable (BMI variation or HOMA-IR variation). For each treatment more points are considered if the treatment is evaluated in multiple studies. The size of the circles is proportional to the number of patients included in the treatment. BAs, bile acids; LAGB, laparoscopic adjustable gastric band; LM, lifestyle modifications; Met, metformin; UDCA, ursodeoxycholic acid

Liraglutide, bile acids, pioglitazone and placebo increased gastrointestinal disorders (81%, 77%, 14.35% and 33.34%, respectively). Bile acids and placebo were associated with itching (14% and 6.5%, respectively). The administration of pioglitazone, bile acids and placebo was associated with pancreatitis (2%, 0.7% and 0.7%, respectively). Rosiglitazone, placebo and pioglitazone treatments were associated with leg swelling (31%, 2.7% and 13%, respectively). Liraglutide, placebo, pioglitazone and bile acid treatments were associated with neurological disorders (14%, 12.47%, 12% and 9.2%, respectively).

4 | DISCUSSION

4.1 | Principal findings

Our study shows that the most effective treatment for NASH is pioglitazone, followed by RYGB and rosiglitazone. Their probabilities of ranking first, second and third in effectiveness were, in fact, 82%, 37% and 16%, independently of the subjects' glycaemic state.

We note that, while rosiglitazone is banned in the European Union, in 2013 the US Food and Drug Administration removed the restrictions on the prescription and use of rosiglitazone, based on data showing an absence of increased cardiovascular risk linked to its use. The results of our meta-analysis are, indeed, intriguing since in the current literature the most important factor correlating with NASH improvement would appear to be weight loss. Conversely, pioglitazone does not induce weight loss, indeed its administration has been associated with moderate weight gain of approximately 5%; however, this fat accumulation favours subcutaneous adipose tissue deposition with reduction of visceral fat.[19] In addition, pioglitazone improves both hepatic and peripheral insulin resistance, and this improvement can play a role in reducing liver fat accumulation and inflammation.[19]

At present, bariatric surgery can be considered in eligible individuals with obesity and NAFLD or NASH, but there are not enough data to consider it as an established option to specifically treat NASH.[3] However, bariatric surgery not only significantly improved histological NAS,[20] but it was also associated with reduced incidence of NASH and hepatocellular carcinoma using a propensity-matched analysis.[21] Moreover, a recent meta-analysis showed that bariatric surgery leads to biopsy-confirmed resolution of steatosis in 66% of patients, inflammation in 50%, ballooning degeneration in 76%, and fibrosis in 40%.[22] The present study demonstrates a beneficial effect on liver histology of RYGB in patients with NASH, but histological RCTs are needed to definitively assess the therapeutic benefits of bariatric surgery in patients with or without obesity and NAFLD and to assess its role in eligible individuals with obesity and established cirrhosis attributed to NAFLD.

In our meta-regression there appears to be a significant correlation between changes in NAS and changes in BMI. However, this relationship seems to be almost entirely driven by studies on bariatric

surgical procedures, where large decrements of BMI occur and where the weight loss may well be the determinant of NAS improvement. It is clear that other treatments may improve NAS through a different mechanism, such as may happen with thiazolidinediones. A common denominator for both RYGB and thiazolidinediones is the improvement of insulin resistance, as confirmed by our meta-regression results showing that each 1% reduction of HOMA-IR index reduced NAS by 0.3% (β = 0.31%, $P < 0.001$).

Drugs currently used to treat NASH belong to four general classes of medications according to their mechanism of action: (a) those that reduce liver fat accumulation; (b) those that reduce liver inflammation and oxidative stress; (c) those that modulate the gut–liver axis; and (d) those that aim to decrease the progression of liver fibrosis and its complications.

The peroxisome proliferator activator receptor (PPAR) family includes α, β/δ and γ agonists. In addition to improving NASH histology, pioglitazone, a PPARγ agonist, reduces the incidence of cardiovascular events in patients with type 2 diabetes and is associated with a reduced mortality when compared with other glucose-lowering agents.[23]

The efficacy of elafibranor, a PPARα/δ agonist, at a dose of 80 or 120 mg/day, to treat biopsy-proven NASH at 1 year, was tested against placebo in the phase IIb GOLDEN-505 RCT.[24]

The drug failed to meet its primary endpoint, namely, reduction of NAS to zero without worsening the degree of fibrosis (progression to stage 3 or 4). A secondary analysis showed that the highest dose of elafibranor tested, 120 mg, was superior to placebo in those subjects with NAS ≥4 (20% vs. 11%; $P = 0.018$),[24] but, because this was not the primary endpoint, this result is merely suggestive.

The class of bile acids also appeared to be promising in the treatment of NASH. Bile acids bind to farnesoid X receptor and, at least in experimental animals, decrease hepatic lipogenesis and steatosis and improve hepatic and peripheral insulin sensitivity. Unfortunately, in humans, 6-ethylchenodeoxycholic acid, or obeticholic acid, proved no better than placebo in the degree of NASH improvement ($P = 0.08$), although fibrosis improved significantly (35% vs. 19%; $P = 0.004$).[25] However, pruritus is a frequent side effect that occurs in 23% of the patients with NASH treated with obeticholic acid at a dosage of 25 mg daily.[25]

The glucagon-like peptide-1 receptor agonist liraglutide 1.8 mg once daily for 42 weeks was shown to induce histological resolution of NASH, defined as disappearance of hepatocyte ballooning without fibrosis worsening, in 39% of patients versus 9% in the placebo group ($P = 0.02$).[26] Although ballooning is a pivotal histological feature of NASH, the above definition of NASH resolution is, however, non-canonical, and in fact NAS did not change significantly with liraglutide compared to placebo (1.3 ± 1.6 vs. −0.8 ± 1.2; $P = 0.24$). Furthermore, the reported number of patients with improvement of NASH histology was 17 (74%) with liraglutide and 14 (64%) with placebo ($P = 0.46$), and the mean changes in hepatocyte ballooning score, steatosis, lobular inflammation and Kleiner fibrosis stage were all not significantly different.[26] For these reasons, in our meta-analysis liraglutide was in fact found to be one of the less effective NASH treatments.

Vitamin E at a daily dose of 800 IU for 96 weeks was found to be superior to placebo in achieving ballooning resolution (placebo vs. vitamin E: 25% vs. 51% improvement; $P < 0.001$),[27] without effects on fibrosis. A safety issue on vitamin E derives from the demonstration that it increases the risk of prostate cancer in elderly men, as shown in the SELECT trial.[28]

Pentoxifylline 400 mg three times daily in a single-centre, open-label RCT including 35 patients determined NAS improvement of 2.10 ± 1.07 compared to placebo (0.90 ± 0.99; $P = 0.006$).[29] However, fibrosis did not improve and further data obtained from large series of patients are needed to assess pentoxifylline effectiveness.

The results of RCTs with drugs acting on fibrosis, such as simtuzumab and cenicriviroc, are disappointing. The phase 2b trial with simtuzumab was prematurely stopped after 96 weeks due to lack of efficacy. Cenicriviroc did not perform better than placebo in achieving the primary endpoint of hepatic histological improvement in NAS by ≥2 points and no worsening of fibrosis.[30]

4.2 | Strengths and limitations of the study

The epidemic dimension of NAFLD, together with the severity of its evolution, call for healthcare providers to be more proactive in finding a treatment. Our network analysis allowed us to make indirect comparisons among over 2300 adult participants, comparing many different treatments, including new drugs, such as elafibranor, simtuzumab, selonsertib, cenicriviroc and liraglutide, which were not considered in previous meta-analyses.[11–13] Furthermore, bariatric surgery was not included in previous meta-analyses.[11–13]

The present meta-analysis provides a credible ranking system for each therapeutic approach to NASH and/or liver fibrosis that is clinically useful.

Another strength of this study is that we focused only on NASH and liver fibrosis rather than on liver steatosis only, and that we rely on liver histology, which is the "gold standard" for NASH diagnosis.

Potential limitations of the present meta-analysis include the lack of RCTs in the field of bariatric surgery and the small number of patients enrolled in lifestyle modification trials. Moreover, some results from our meta-analysis could be affected by low statistical power while some other comparisons may incorrectly indicate a strong evidence. This is a general shortcoming of NMAs, which typically involve a multitude of comparisons and use evidence from indirect comparisons. In the present study, for example, while the size of the effect of a treatment is estimated on the basis of potentially strong evidence, depending on the number of studies and patients involved, comparisons derived from indirect evidence could in principle be affected by low power. This is the case for comparisons involving RYGB and LAGB, for which direct evidence allows the main effects to be estimated and comparisons made, while indirect comparisons with any other treatment in the network cannot be made because of the absence of a control group. Moreover, since these two treatments are unconnected in the network they cannot be included in the network inconsistency analysis. Rigorous power analyses should

be carried out even if the power and precision of indirect evidence are more difficult to assess than using direct evidence.[31] Despite these limitations, the estimated efficacy of RYGB derives from studies including a large number of patients (399 subjects). A low power may also allow a potentially effective therapy from the sub-analysis conducted on the percentage of responders (responders are defined as having a reduction of at least two points of NAS) to be discarded. In fact, the analysis failed to reveal any significant effect of the treatments. While this result may be due to low power (the analysis was performed in 14 studies and 11 treatments), only the studies comparable in terms of responders and, therefore, homogeneous were included in the analysis.

4.3 | Possible pharmacological and pathophysiological explanation for the effects of pioglitazone and antioxidants

It is largely recognized that PPARγ agonists, such as pioglitazone, increase insulin-mediated glucose disposal by almost 30%,[32] thus improving whole-body insulin resistance. Pioglitazone acts also by stimulating expansion of "metabolically healthier" adipose tissue and by redirecting triglycerides from the liver to the subcutaneous fat compartment. Moreover, because pioglitazone is a partial PPARα agonist, it enhances hepatocyte fatty acid oxidation and reduces triglyceride accumulation in the liver.[33] In the liver PPARγ reduces the expression of proinflammatory cytokines while it enhances the expression of anti-inflammatory and proresolving cytokines.[34,35] Therefore, pioglitazone not only reduces liver steatosis but also decreases liver inflammation.

When the level of reactive oxygen species in the liver is too high it causes oxidative stress that mediates the progression of liver fibrosis.[36] Antioxidants reduce the oxidative stress and consequently lessen liver fibrosis progression.

4.4 | Conclusions and policy implications

In conclusion, bearing in mind the limitations mentioned above, pioglitazone followed by bariatric surgery and, in particular, RYGB, are the most promising therapeutic approaches to treat NASH. Antioxidants seem to be effective in reducing liver fibrosis. A reduction of 1% in BMI could reduce the histological NAS by 1.3%, and a 1% reduction in hepatic insulin resistance could reduce NAS by 0.3%. Therefore, weight loss and improvement of hepatic insulin resistance are the most promising approaches in the treatment of NASH.

Our NMA offers new evidence to scientific societies for developing clinical practice guidelines. We provide a quantitative comparison of interventions that were not directly compared in previous trials.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

S.P., G.M. and S.R.B. conceived and designed the study. O.V., S.P. and L.L.A. selected the articles and extracted the data. S.P. and S.M. analysed the data. S.P., O.V., S.R.B. and G.M. wrote the first draft of the manuscript. S.P., S.B., O.V. and G.M. are guarantors of the data. All authors interpreted the data and contributed to the writing of the final version of the manuscript. All authors agreed with the results and conclusions of this article.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14304.

DATA AVAILABILITY STATEMENT

Data are available for use in collaborative studies to researchers upon reasonable request (geltrude.mingrone@unicatt.it). Data will be provided following the review and approval of a research proposal (including a statistical analysis plan) and completion of a data-sharing agreement. Responses to the request for the raw data will be judged by a committee including G. Mingrone, S. Panunzi and S. Bornstein.

ORCID

Geltrude Mingrone https://orcid.org/0000-0003-2021-528X

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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